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Pigmentary Abnormalities in Genetic Disorders

*Anne W. Lucky, M.D.**

There are a large number of genetic disorders in which pigmentary abnormalities are prominent features and which have been reviewed extensively.[10, 18, 26, 34, 47, 69] This article focuses on a few of the most common genetically inherited disorders of pigmentation.

MULTIPLE LENTIGINES SYNDROMES

LEOPARD Syndrome

The multiple lentigines or LEOPARD syndrome is an autosomal dominant disorder with variable expressivity. It is rare, but the cutaneous findings are so distinctive that the diagnosis should not often be missed.[19, 20, 39, 46, 60, 61, 62, 68] Affected patients develop multiple hyperpigmented macules usually starting during early infancy to mid childhood and stabilizing at puberty. Rarely, lesions are present at birth.[30] These lesions can range in color from speckled light brown to nearly black, often depending on the underlying general pigmentation. Individual lesions tend to be small, less than 1.5 cm, and are often interspersed with a few larger, darker lesions. Mucous membrane surfaces are spared. When these lentigines are light in color, they may be confused with ephilides (freckles). However, their appearance in non–sun-exposed areas such as the buttocks, inner surfaces of the arms and legs, and axillae and the fact that they do not darken on sun exposure differentiate them from ephilides (Fig. 1*A*). Biopsy reveals the characteristic features of lentigines, including basal-layer hyperpigmentation and thin, downward elongations of the rete pegs. There have been some reports of giant melanosomes in the lentigines of LEOPARD syndrome, but their significance is uncertain.[5, 70] The eponym LEOPARD[19] stands for *l*entigines, *E*KG abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of the genitalia (including hypospadias and cryptorchidism), *r*etardation of growth, and sensorineural *d*eafness (Table 1). Other features described in these patients have been summarized in recent reviews.[39, 62] Specific cutaneous features that have been found include axillary freckling, café-au-lait spots (Fig. 1*B*), localized hypopigmentation, abnormal dermatoglyphics, interdigital webs, onychodystrophy, hyperelasticity of the skin with joint laxity, and multiple granular-cell myoblastomas. Although some children have also been reported to have mental retardation, this may be secondary to lack of early recognition of the deafness. Oddly enough, there have been patients reported with the noncutaneous manifestation of this syndrome without the lentigines.[20]

NAME and LAMB Syndromes

These mnemonics describe an overlapping group of pigmentary disorders associated with atrial myxomas that actually appear to be quite distinct from the LEOPARD syndrome. The term NAME syndrome (*n*evi, *a*trial myxomas, *m*yxoid neurofibromas, and *e*phelides) was coined by Atherton and associates in 1980,[2] although earlier cases had been published in

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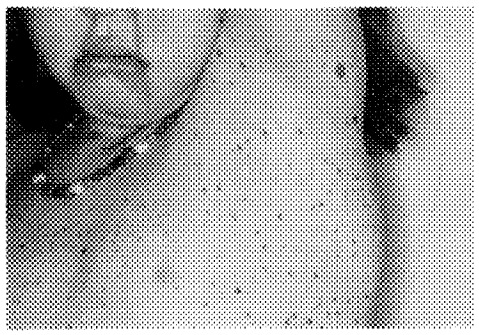

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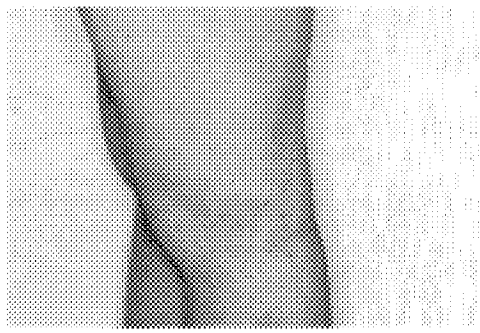

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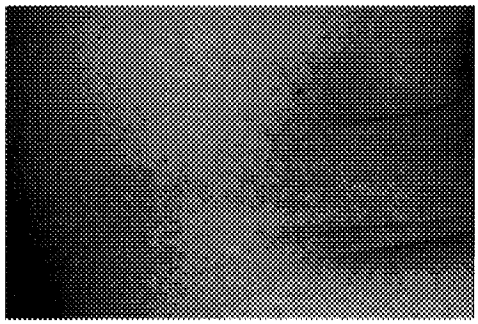

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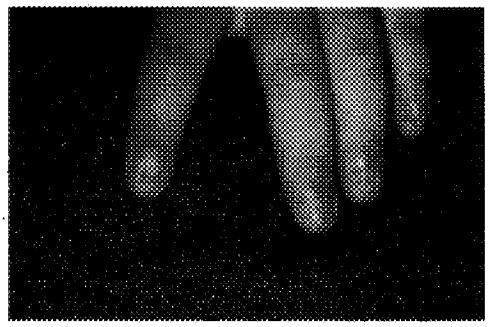

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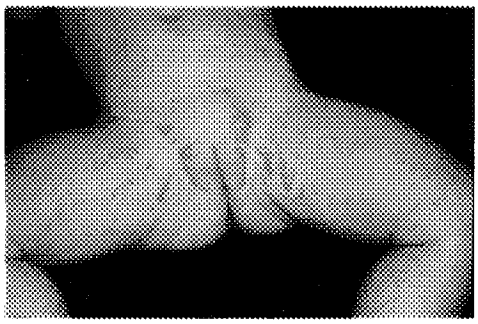

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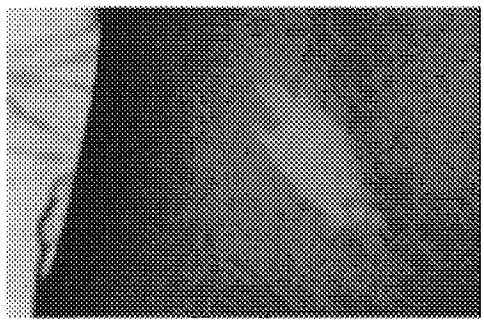

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Figure 6A.

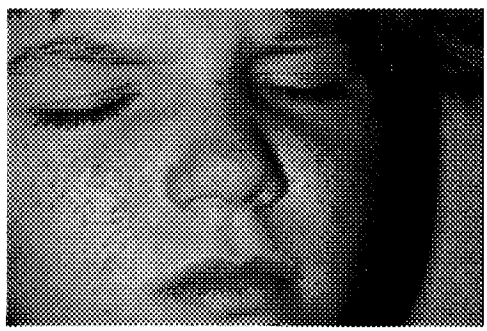

Figure 6B.

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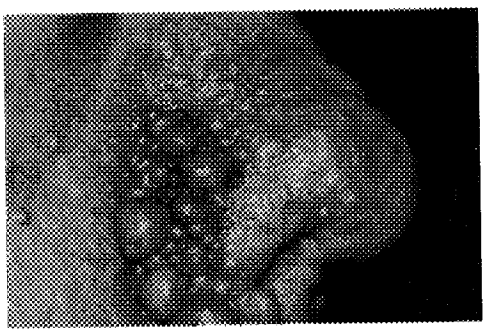

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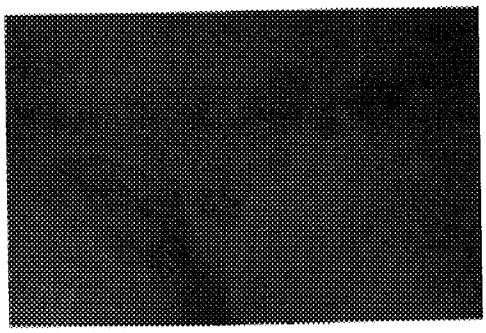

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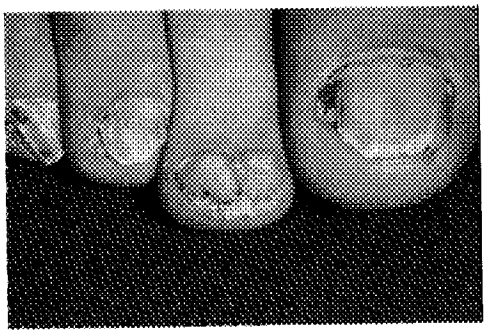

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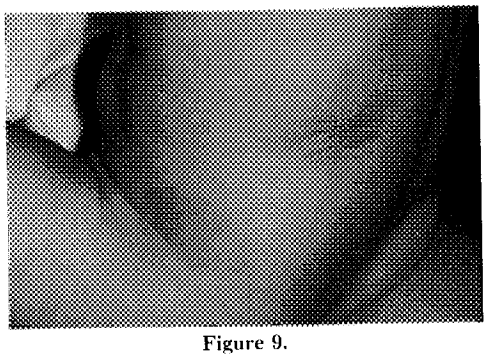

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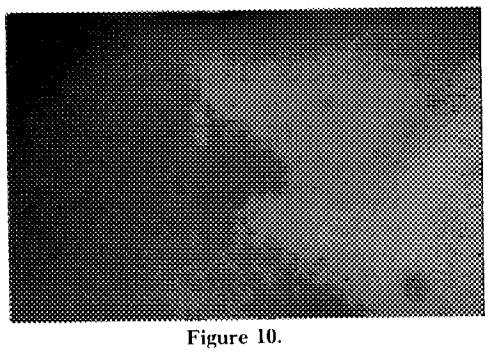

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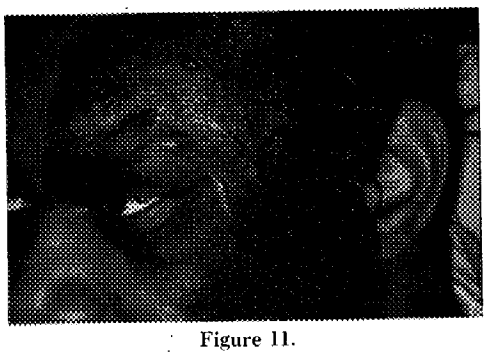

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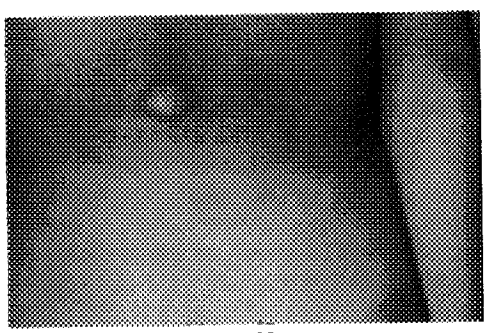

Figure 12.

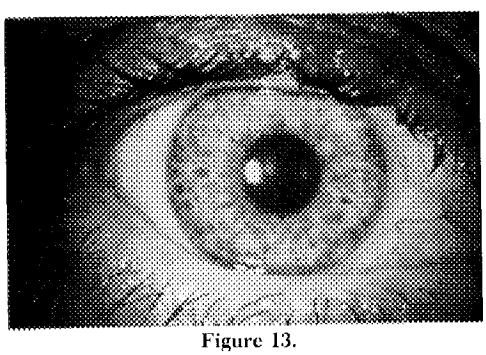

Figure 13.

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Table 1. *LEOPARD Syndrome*

Lentigines
EKG abnormalities
Ocular hypertelorism
Pulmonary stenosis
Abnormalities of the genitalia (hypospadias, cryptorchidism)
Retardation of growth
Deafness, sensorineural

the literature. Their patients had a profusion of nevocellular nevi, ephilides, and domed blue nevi. No lentigines were found. Lesions appeared at birth or in early infancy. In contrast to the LEOPARD syndrome, the axillae were spared, and lesions were abundant on the mucosal surfaces. The first patients reported had red hair and fair skin.

At about the same time, similar patients were reported by Rhodes and coworkers;[51] these patients had widespread mucosal lentigines rather than nevi and cutaneous myxomas rather than neurofibromata in association with atrial myxomas (the LAMB syndrome: *l*entigines, *a*trial myxoma, *m*ucocutaneous myxomas, and *b*lue nevi).[15, 50] These patients did not appear to have the other skeletal, cardiac, and cutaneous abnormalities or sensorineural deafness associated with LEOPARD syndrome, but a recent report describes associated intracerebral aneurysms.[45] Future reports of more cases of this rare disorder may help to clarify the range of pigmented lesions associated with atrial myxomas (Table 2).

Congenital and Acquired Multiple Lentigines

Congenital or acquired multiple lentigines may occur without any other associated cutaneous or systemic abnormalities.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome is the eponym for gastrointestinal polyposis with mucocutaneous lentigines.[24, 25] It is an autosomal dominant condition heralded by the appearance of brown to black to blue macules that may be present at birth or appear in early infancy or childhood. The pigmented macules have a characteristic distribution around the mouth, lips, and buccal mucous membranes as well as being scattered around the nose and on the face. In addition,

Table 2. *Pigmentary Disorders Associated with Atrial Myxomas*

NAME
Nevi
Atrial myxoma
Myxoid neurofibroma
Ephilides
LAMB
Lentigines
Atrial myxoma
Mucocutaneous myxomas
Blue nevi

Figure 1. A 5-year-old girl with multiple lentigines syndrome. *A*, Note that dark brown macules extend into the axilla in non–sun-exposed areas. *B*, Associated lighter-brown café-au-lait spots on the lower extremities. This child also had EKG abnormalities and short stature.

Figure 2. A 12-year-old boy with dyskeratosis congenita showing confetti-like, mottled hyperpigmentation and hypopigmentation over the flank.

Figure 3. Typical nail dystrophy in a patient showing longitudinal splitting and reabsorption of nail plate with proximal pterygium formation (same patient as in Figure 2). Eventually, all nails may be lost in dyskeratosis congenita.

Figure 4. Incontinentia pigmenti in a 2-year-old girl demonstrating swirled "marble cake" hyperpigmentation on the trunk and extremities. This child's mother had a single linear streak of hyperpigmentation on the leg.

Figure 5. Typical "ash-leaf" spot of tuberous sclerosis. These hypopigmented macules are usually present at birth.

Figure 6. Angiofibromas on the face have acquired the misnomer of adenoma sebaceum. They can be mild, barely noticeable, flesh-colored papules (*A*), primarily vascular lesions for which hemorrhage is a primary problem (*B*), or severe, disfiguring nodules (*C*).

Figure 7. Typical shagreen patch, which is a collagenoma typically located, as in this case, over the sacrum in patients with tuberous sclerosis.

Figure 8. Periungual and subungual fibromata with longitudinal splitting of the nails is also characteristic of adults with tuberous sclerosis.

Figure 9. Typical smooth-bordered café-au-lait spot over the hip in an infant with neurofibromatosis. There is also a localized area of hypertrichosis not uncommonly seen in this disorder.

Figure 10. Large, irregularly bordered, hyperpigmented macule over the hip in a young man with neurofibromatosis. Two café-au-lait spots are also seen. Such large pigmented patches often overlie plexiform neurofibromatas.

Figure 11. A 30-year-old man with a single hyperpigmented macule overlying a plexiform neurofibroma on left upper quadrant of his face and scalp. This lesion has required resection three times to preserve vision. This patient had no other stigmata of neurofibromatosis and has segmental neurofibromatosis.

Figure 12. Multiple café-au-lait spots on the back with large hyperpigmented macule over the sacrum. There is a large neurofibroma centrally. Such sacral lesions may be indicators of spinal cord involvement.

Figure 13. Iris (Lisch) nodules, which are pigmented lesions on the iris of this patient with neurofibromatosis. These nodules are present in more than 90 per cent of patients with neurofibromatosis and appear after age 6.

lesions appear on the fingers and toes on both palmar and volar surfaces. The lesions are characteristically absent on extensor and flexor surfaces of the rest of the body. These lesions are less than 1 cm in diameter, remain discrete macules, and are not affected in size or color by sunlight. In contrast to ephilides, they characteristically appear in dark-skinned individuals. The cutaneous, although not the mucosal, lesions may fade at puberty. Histologically, the skin lesions show basal cell–layer hyperpigmentation but lack the downward projection of the rete ridges seen in typical lentigines.[32] Clinically, however, they do resemble lentigines.

The importance of these cutaneous lesions is that they herald mucosal polyposis of the entire bowel. Jejunal lesions are the most characteristic. These lesions do not have a predisposition to malignant transformation but represent hamartomas. The principal clinical problem associated with the polyposis is intussusception, bleeding, and subsequent anemia.

DYSKERATOSIS CONGENITA (Zinsser-Cole-Engman Syndrome)

Dyskeratosis congenita is a rare disorder usually affecting only males and inherited as an X-linked recessive trait.[11, 23, 63, 73] There have been a few autosomal dominant kindreds reported in which female patients have also been affected.[66] The syndrome is characterized by a triad of reticulated hyperpigmentation and hypopigmentation, nail dystrophy, and mucous membrane leukoplakia. The striking pigmentary abnormality is a gradual progressive appearance of reticulated, less than 1 cm, hyperpigmented, gray to brown macules on an atrophic and often hypopigmented background (Fig. 2). It has been described as similar to poikiloderma vasculare atrophicans. Lesions characteristically appear first in flexural locations such as the sides of the neck and the groin; the trunk, face, and shoulders can then be affected. Initially, the skin may just appear "dirty" and refractory to cleansing. There is no hyperkeratosis or scale. Other cutaneous manifestations include bullae on the palms and soles initiated by trauma and hyperkeratosis and hyperhidrosis of the palms and soles. Hair on the scalp and the eyebrows and eyelashes may become sparse or absent. Biopsy of typical skin lesions reveals epidermal atrophy and upper dermal melanophages.

A second major manifestation is leukoplakia of the oral and other mucosal surfaces. Such leukoplakia may appear as early as the teenage years but most commoly appears after the third decade. Oral erosions have been reported in early childhood and may precede the leukoplakia. Such lesions are premalignant, often degenerating into squamous cell carcinomas.

Table 3. *Manifestations of Dyskeratosis Congenita*

Cutaneous	
Pigmentary	
	Reticulated macular hyperpigmentation and hypopigmentation with atrophy
Nonpigmentary	
	Mucosal leukoplakia (premalignant)
	Longitudinal ridging and hypoplasia of nails
Noncutaneous	
Aplastic anemia and/or pancytopenia	
Mild mental retardation	
Muscular atrophy of hands and feet	
Lacrimal duct obstruction	
Ectropion	
Dental dystrophies	
Cataracts	
Frequent infections	
Malignancies	

The third cutaneous manifestation is severe nail dystrophy, which may be the primary manifestation, preceding the others. Nail plates are characteristically small, hypoplastic, or even absent. The initial findings include striking longitudinal ridging, pterygia, and eventual resorption (Fig. 3). Noncutaneous features of the condition are listed in Table 3. Cataracts are rarely present.[36] Marrow hypoplasia with aplastic anemia or pancytopenia, severe sudden infections, and generalized malignancies often significantly shorten the life expectancy.

The underlying abnormality in this disorder is not well understood. Although there is no evidence of increased numbers of spontaneous chromosomal breaks, extensive cross-linking of DNA and increased numbers of sister chromatid exchanges in cultured skin fibroblasts exposed to trimethylpsoralen and ultraviolet light have been demonstrated in two unrelated patients.[7]

INCONTINENTIA PIGMENTI

Incontinentia pigmenti, or the Bloch-Sulzberger syndrome, is one of the few pigmentation disorders inherited as an X-linked dominant trait.[6, 26] This mutation is presumed to be lethal to the male XY fetus because predominantly females are affected. There have been a few phenotypically similar cases reported in males that are presumed to be the result of spontaneous mutation, but chromosomal anal-

ysis has revealed at least two patients with XXY Klinefelter's syndrome.[28, 42] Some authors have considered this to be an autosomal dominant disorder limited primarily to females. In the typical inheritance pattern, an affected female will have a 50 per cent chance of having an affected daughter and presents no risk to her male offspring. There is also an increased rate of spontaneous abortion of 50 per cent of potential male fetuses.

The disease exists in three stages. Stage 1 presents at birth or within 2 (90 per cent) to 6 (96 per cent) weeks. Linear vesicular lesions appear most often on the extremities. Histologically, these lesions are composed of unique intraepidermal eosinophilic vesicles that resolve over a period of weeks. In stage 2, the areas affected by the vesicular lesions gradually become linear verrucous streaks. Exacerbation of vesiculation may occur with intercurrent viral illnesses. The peak time of onset is 2 to 6 weeks of age. The lesions often fade again in a period of weeks, although they may persist for years. Finally, in the permanent stage 3, the onset of which is between 12 and 26 weeks of age, macular hyperpigmented whorls and streaks, which have been described as looking like a marble cake, appear at any location on the body but not necessarily at the site of previous vesicular or verrucous lesions (Fig. 4). In fact, there is a predilection for the trunk rather than the extremities in stage 3. Oddly enough, some babies (14 per cent) are born manifesting the second, third, or both stages of incontinentia pigmenti and are presumed to have passed through the earlier stages in utero, although there is no evidence that this has happened. All three stages may appear together. Recently, a stage 4, consisting of atrophy, depigmentation, and eventual fading of hyperpigmented lesions, has been reported in older patients.

The diagnosis is most easily made histologically in stage 1 because of the unique intraepidermal eosinophilic vesicles. In stage 3, there is a very bland postinflammatory hyperpigmentation with incontinent pigment in macrophages in the upper dermis. Other cutaneous findings include sparse hair, especially at the vertex, and conical or missing teeth.

The principal clinical significance of incontinentia pigmenti lies in the associated ocular, dental, and neurologic abnormalities (Table 4). Seizures and psychomotor and mental retardation may be severe and are important to mention in genetic counseling because they can occur in the offspring of a parent who has only the skin manifestations.

Table 4. *Manifestations of Incontinentia Pigmenti*

Cutaneous
Pigmentary
Whorls and linear streaks of hyperpigmentation ("marble cake") (stage 3, trunk and extremities)
Nonpigmentary
Conical and/or missing teeth
Linear vesiculation of extremities (stage 1)
Linear verrucous extremities (stage 2)
Alopecia (38%)
Noncutaneous
CNS disturbances (30%)
Seizures (13%)
Psychomotor retardation (17%)
Mental retardation (16%)
Eosinophilia, leukocytosis
Dental abnormalities
Partial or complete anodontia
Conical "pegged" teeth
Strabismus, other eye abnormalities (35%)

A disorder often confused with but not related to incontinentia pigmenti is hypomelanosis of Ito, which has been given the cumbersome name "incontinentia pigmenti achromians." This is an ill-defined, possibly autosomal dominant, neurocutaneous syndrome with typical hypopigmented lesions of incontinentia pigmenti but in a "negative image." Both males and females can be affected, and there is usually profound mental retardation. There are many associated abnormalities, usually related to the central nervous system, but these patients do not present as specific a syndrome as those with incontinentia pigmenti itself.

TUBEROUS SCLEROSIS (Epiloia, Bourneville's Disease, Pringle's Disease, Hamartomatosis)

Tuberous sclerosis is an autosomal dominant disorder affecting multiple organ systems with hamartomatous growth.[9, 22, 29, 37, 43, 49] As in many other autosomal dominant disorders, there is a wide spectrum of clinical expression and a relatively high spontaneous new mutation rate, said to be nearly 60 per cent. This estimate may be high, however, because some affected parents may not have obvious clinical manifestations, and careful evaluation will reveal asymptomatic affected individuals.[8] The estimated prevalence is 1 in 300,000.

The most serious consequences of tuberous sclerosis are the neurologic ones: seizures, especially infantile spasms, malignant brain tumors, and mental retardation may be severe,

Table 5. *Manifestations of Tuberous Sclerosis*

Cutaneous	
Pigmentary	
	Ash-leaf spot
	Poliosis
	Hypopigmented spots on iris
	Gingival fibromas
Nonpigmentary	
	Angiofibroma (appearing late in childhood)
	Shagreen patch
	Periungual fibromas (appearing late in childhood)
	Alopecia (patches)
Noncutaneous	
CNS abnormalities: seizures, retardation, tumors, (hamartomas of grey matter, subependymal nodules, astrocytomas), hydrocephalus, intracranial calcifications	
Retinal phakomas (hamartomas)	
Sclerosis of skull and long bones with or without cysts	
Renal hamartomas (angiomyolipomas, angiomyofibromas, cysts)	
Cardiac rhabdomyomas (multiple)	
Pulmonary disease (cystic fibromyomata)	

even life-threatening. Not all patients have central nervous system problems, however. The noncutaneous manifestations of tuberous sclerosis are listed in Table 5.

The best known cutaneous finding is the "ash-leaf" spot.[16] These lesions appear as one or several hypopigmented to depigmented macules or patches scattered anywhere on the trunk or extremities and resemble in shape the leaf of the mountain ash (Fig. 5). These lesions have been said in most of the literature to be present at birth, although they are sometimes difficult to see even with the extra contrast afforded by the Wood's light. There is also evidence from careful longitudinal studies that lesions may appear later in life.[41] Depigmented macules are estimated to be present in 80 to 95 per cent of individuals with tuberous sclerosis.[22, 41] In addition to the typical ash-leaf configuration, rounded at one end and pointed at the other, lesions may be confetti-like or dermatomal in distribution.

Histologically, there is a normal number of melanocytes, distinguishing the lesions from vitiligo, but a decrease in the number and size of melanosomes.[16] Similar losses of pigment can also occur in hair-bearing areas, resulting in poliosis of the scalp, eyelashes, or eyebrows. Several cases have been reported in which poliosis has preceded the appearance or at least the recognition of cutaneous depigmented spots.[35] Similarly, small white spots on the iris[21] and retina[9] have been reported and postulated to be analogous to the cutaneous ash-leaf spots.

Although it has been said in many reviews that patients with tuberous sclerosis have an increased number of café-au-lait spots, careful study and review of the literature have revealed that the incidence is no higher than that in the general population, approximately 16 per cent.[4] A few cases have been reported with coexistent tuberous sclerosis and neurofibromatosis. Other cutaneous, although nonpigmented, lesions characteristic of tuberous sclerosis are angiofibromata of the face. The older term "adenoma sebaceum" is misleading, because these lesions are neither adenomatous nor sebaceous. Angiofibromas appear in 70 to 80 per cent of affected patients, developing after age 4. They are usually initially clustered around the nasolabial folds and then spread out onto the cheeks, chin, and forehead during adolescence, when their numbers appear to stabilize. Lesions range from tiny, flesh-colored papules, with or without small overlying telangiectasias (Fig. 6*A* and *B*), to large, pedunculated or sessile, pink to purple nodules studded with superficial telangiectasias (Fig. 6*C*). They may remain so small that they are not recognized as being abnormal and are ignored by the patient, or they may become quite disfiguring. Temporary cosmetic improvement can be achieved with the argon laser[1] as the preferred modality, although other destructive therapies, including the CO_2 laser, dermabrasion, electrodesiccation, and cryotherapy have been advocated.

Another congenital lesion, the shagreen patch, is a hamartoma of collagen presenting as a soft, flesh-colored, infiltrated plaque that is over the sacrum in 35 to 48 per cent of patients. The lesions have a characteristic pigskin or peau d'orange surface and are infiltrated plaques with accentuated follicular orifices (Fig. 7). Such lesions may also be seen in patients without tuberous sclerosis. Histologically, they are collagenomas. Periungual fibromas also appear around adolescence in 9 to 20 per cent of individuals and are fibrous, flesh-colored nodules growing adjacent to or beneath the nails on both fingers and toes (Fig. 8).

NEUROFIBROMATOSIS

Neurofibromatosis is an autosomal dominant disorder affecting multiple organ systems. It is quite frequent, occurring in 1 in 3000 individuals, and has a very high spontaneous rate of mutation, such that more than half of the cases represent new mutations. Although it has a high degree of penetrance, there is very wide variation of expressivity. Indeed, the spectrum

of manifestations is staggering. Only cutaneous and, especially, pigmentary disorders will be discussed in this article; several comprehensive reviews have appeared in the literature.[12, 52, 53, 54, 57, 59] It is rare that such a large volume of data on a single disease is accumulated by one investigator, but Dr. Vincent Riccardi at Baylor University in Texas has seen many patients and amassed a large amount of data about neurofibromatosis, which has recently been published in a volume that serves as the definitive text on this disorder.[56]

Of the cutaneous signs of neurofibromatosis, the best known and premier is the café-au-lait spot. Crowe, in 1956, first reported that the presence of six or more café-au-lait spots greater than 1.5 cm in diameter was pathognomonic of neurofibromatosis (i.e., 90 per cent of the normal population have fewer than this number). The spots are usually present at birth or appear shortly thereafter and will usually be present by 1 year of age if they are to appear at all.[56] Clinically, café-au-lait spots are light tan to brown macules with relatively regular borders, often having an oval shape (Fig. 9). It has been said that the pigmented macules seen in Albright's polyostotic fibrous displasia have more jagged borders and are distinguishable, but this has been disputed.[57] A more difficult differential diagnosis may be a congenital or acquired lentigo, which usually does have a more jagged border but can often be distinguished histologically from a café-au-lait spot.

The histologic appearance of the café-au-lait spot has been disappointing, appearing much like normal skin with some increased basal layer pigmentation. Although there has been some interest in the presence of giant melanosomes in the spots,[38] such structures have been seen in normal skin from patients with neurofibromatosis as well as in normal skin of unaffected persons.[17, 56] Affected patients, especially children, may have no giant melanosomes in their spots. Thus, diagnostically, giant melanosomes are not useful markers.

A second pathognomonic feature has been so-called axillary freckling. This term may be a misnomer, as freckles are sun-induced hyperpigmented macules whereas the lesions in neurofibromatosis appear in shaded, intertriginous areas. They are not present in infancy but develop with age and seem to be related to friction in such flexural areas as axilla and groin and under the breast. The association of at least six café-au-lait spots with axillary freckling may indeed be absolutely pathognomonic of neurofibromatosis.

Another characteristic, but less well recognized, sign of neurofibromatosis is the presence of large hyperpigmented patches with relatively regular borders overlying plexiform neurofibromas. These lesions tend to be more hyperpigmented than the ordinary café-au-lait spot and are sometimes hypertrichotic (Figs. 10 and 11). The histology of such patches has not been characterized. However, their presence should alert one to the potential presence of an internal and possibly invasive plexiform neurofibroma. When located across the midline in the back, spinal cord involvement should be considered strongly (Fig. 12).

In addition to the specific pigmentary disorders described above, patients with neurofibromatosis seem to have a tendency to acquire large numbers of other common pigmented lesions such as nevocellular nevi and lentigines. There is also a poorly defined but well-recognized diffuse hyperpigmentation. The origin of stimulation for these pigmented lesions has not been clear, but it has been postulated by Riccardi to be related to the excessive number of mast cells seen in this disorder. Such an association may be analogous to what one sees in cutaneous mastocytosis, where clusters of mast cells are associated with pigmentation. In neurofibromatosis, however, the mast cells are not clustered but rather diffusely present in excessive numbers throughout the skin, especially around areas of growing neurofibromas.[56]

Described later than the café-au-lait spot, but possibly a more pathognomonic feature of neurofibromatosis, is the pigmented raised iris nodule described by Lisch.[33, 56, 72] These lesions are melanocytic hamartomas. Such nodules are not congenital and appear in 94 per cent of patients after the age of 6 years. They are probably more common in adults than are café-au-lait spots, making them a more reliable indicator of the presence of neurofibromatosis. Because these are three-dimensional lesions, they are best seen through a slit lamp for accurate diagnosis to distinguish them from other pigmentary lesions on the iris (Fig. 13).

Other nonpigmented cutaneous lesions associated with neurofibromatosis include neurofibromas and plexiform neurofibromas. Neurofibromas are composed primarily of Schwann cells and fibroblasts with a smattering of perineural and endothelial and very small numbers of neuronal cells. Mast cells are abundant around such lesions. These nodules range in size from millimeters to centimeters and may be sessile or, when present a long time, pedunculated. They tend to appear around the time

Table 6. *Manifestations of Neurofibromatosis*

Cutaneous	
Pigmentary	
	Café-au-lait spots
	Axillary (intertriginous) "freckling"
	Iris (Lisch) nodules
	Large pigmented macules overlying plexiform neurofibromas
	General hyperpigmentation
	Hypopigmented macules (rare)
Nonpigmentary	
	Neurofibromas
	Plexiform neurofibromas
	Angiomas
	Juvenile xanthogranulomas
	Blue-red macules
	Atrophic hypoplastic macules (rare)
	Segmental hypertrophy
	Pruritus
Noncutaneous	
CNS	
	Macrocephaly
	Tumors (opic gliomas, acoustic neuromas, astrocytomas, meningiomas, neurolemmomas)
	Delayed development, learning disorders, retardation
	Seizures
Skeletal	
	Pseudoarthrosis
	Kyphoscoliosis
	Short stature
Endocrine	
	Precocious/delayed puberty
	Pheochromocytoma
Malignancies	
	Neurofibrosarcoma, malignant schwannoma
	Neuroblastoma, Wilms' tumor, rhabdomyosarcoma, leukemia
Miscellaneous	
	Constipation
	Hypertension

Table 7. *Classification of Neurofibromatosis*

I.	Classical (von Reckinghausen)
II.	Acoustic
	Bilateral acoustic neuromas
	Few if any cutaneous signs
	Autosomal dominant
III.	Mixed
	Combined I and II
IV.	Atypical, unclassified
V.	Segmental (localized)
	Probably not inherited
VI.	Café-au-lait spots only
VII.	Neurofibromas only
	Appear in third decade; not familial

Modified from Riccardi VM, Eichner JE: Neurofibromatosis: Phenotype, Natural History, and Pathogenesis. Baltimore, The Johns Hopkins University Press, 1986.

of puberty, and their numbers may increase dramatically during pregnancy. These are usually soft, flesh-colored, violaceous or slightly hyperpigmented, sometimes rubbery-feeling nodules that characteristically "button hole" into the skin when depressed. Eighty-five per cent of women with neurofibromatosis will develop areolar neurofibromas by 20 years of age. Cutaneous neurofibromas can undergo malignant degeneration to neurofibrosarcomas.

Plexiform neurofibromas represent large hamartomas that are huge masses that can track into internal organs in the thorax or abdomen or invade soft tissues, with massive soft-tissue overgrowth (Figs. 14 and 15). They may appear as soft, doughy "bags of worms." Surgical excision may be difficult or impossible. As noted above, there is often a characteristic overlying hyperpigmented patch. These lesions are usually, if not always, congenital, but progressive growth may make them more apparent later in childhood or adult life. Blue-red macules that histologically show thick-walled blood vessels[71] and pseudoatrophic macules[71] or dermal hypoplasia,[40] representing neurofibromatous replacement of collagen in the dermis associated with abnormal autonomic vascular regulation, are cutaneous features of neurofibromatosis recently recognized as distinctive. Finally, a significant clinical symptom of neurofibromatosis in at least 10 per cent of patients is severe pruritus, episodes of which are often associated with outbreaks of multiple neurofibromas. Recent evidence again points toward the mast cell as a mediator of this pruritus. In early clinical trials, the mast cell inhibitor ketotifen shows promise for relief of pruritus as well as for prevention of growth and perhaps even induction of regression of neurofibromas.[58] Other manifestations of neurofibromatosis are listed in Table 6.

Riccardi has subclassified neurofibromatosis into seven types (Table 7). Most of the above discussion concerns type I (generalized) neurofibromatosis, as described by von Recklinghausen. It is important to distinguish this type from others such as type V (segmental), which do not have the same prognostic significance.

Other cutaneous lesions that have been described rarely in neurofibromatosis are hypopigmented lesions. These may be oval or lancet shaped, similar to the ash-leaf spot of tuberous sclerosis. There have also been reports of small guttate macules, usually on the lower extremities. Atrophic macules associated with tenderness have also been reported. In early to mid adult life, angiomas of various kinds are not

uncommon. Finally, xanthogranulomas appear to be more frequent in neurofibromatosis than in the general population of children. The association of juvenile xanthogranulomas with café-au-lait spots has been linked to a higher incidence of leukemia. In fact, the association of neurofibromatosis with increased risk for a variety of malignant neoplasms, especially of the central nervous system, has recently been documented.[3, 65]

Despite the large number of affected patients and the well-known manifestations of this disease, little is understood about its pathogenesis. Studies on collagen structure and composition,[44, 67] growth factors,[55, 64] and characteristics of cultured cells[27] may be fruitful leads toward future understanding.

ALBRIGHT'S POLYOSTOTIC FIBROUS DYSPLASIA (Albright's Disease, McCune-Albright's Disease)

Albright's polyostotic fibrous dysplasia is a very rare, sporadic disorder that can be confused with neurofibromatosis and thus is included in this article.[14, 31, 57] These patients have characteristic pigmentary changes that may be present at birth or appear in childhood. The lesions are large, tan to brown, hyperpigmented patches that are indistinguishable from the café-au-lait spots seen in neurofibromatosis. It was said in the past that the borders of these macules are relatively more jagged, like the coast of Maine, than in neurofibromatosis, where they are smoother, like the coast of California, but this may be an overstatement. In general, the lesions of polyostotic fibrous dysplasia tend to be larger and localized to the trunk and extremities, sparing the face. The other characteristic hallmarks of this disease are fibrous pseudocysts of the long bones, hyperostotic lesions of the skull, and true isosexual precocity. Significant complications of the disorder relate to bony fractures and precocious puberty. The latter may be treated successfully with an aromatase (estrogen synthesis) inhibitor, testolactone.[15]

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